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Poor Oral Health as a Risk Factor for Esophageal Squamous Dysplasia in Northeastern Iran

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Abstract. *Background: Northeastern Iran has one of the highest rates of esophageal squamous cell carcinoma (ESCC) in the world. The reasons for observing such high rates of ESCC in this area are not fully clear. The current study evaluates the association between some potential risk factors and squamous dysplasia, a precursor lesion of ESCC, in northeastern Iran. Materials and Methods: Using logistic regression, we compared potential risk factors of ESCC in 124 individuals with dysplasia and 50 normal individuals from northeastern Iran. Case/control status was histologically proven in all 174 study participants. Results: Poor oral health showed a dose-response association with ESCC risk (p for trend < 0.01). Edentulous individuals had 5-fold higher risk of dysplasia compared to participants with good oral health (p-value < 0.01). Conclusion: Our results are consistent with two other published studies that have shown oral health as a risk factor for ESCC. The high incidence of ESCC in northeastern Iran may be partly attributable to poor oral health.*

The Turkoman plain in the Caspian Littoral of northeastern Iran was identified as an exceptionally high incidence area for esophageal squamous cell carcinoma (ESCC) and squamous dysplasia in the early 1970s, with ESCC incidence rates of more than 100/100,000 in both men and women, some of the highest incidence rates observed for any type of cancer in the world (1,2).

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An international collaborative project was started in the 1970s to evaluate the role of environmental risk factors in the etiology of ESCC in this area, beginning with several ecological studies followed by one well designed case-control study. While the epidemiological studies showed geographical differences in several factors between high- and low- incidence areas in the Caspian Littoral, the case-control study identified only low socioeconomic status and low consumption of fruits and vegetables as risk factors for ESCC (3-5). Unfortunately this series of studies was discontinued 25 years ago due to sociopolitical changes in Iran, without further confirmation of the results.

The current study presents the results of a more recent effort to re-evaluate the risk factors of ESCC in northeastern Iran. This study is part of a new international effort to assess the recent incidence patterns, to elucidate the etiology, and to find early detection markers of ESCC in the Turkoman region.

Materials and Methods

In 1995 and 1996, we conducted a balloon cytology/chromoendoscopy screening study in the Turkoman plain to assess current incidence patterns and to evaluate the feasibility of balloon cytology as a screening procedure in this population (6). This study was approved by the Ethics Committee of the Research Department of the Iranian Ministry of Public Health, and all participants signed an informed consent. As a part of this study, we administered a structured questionnaire covering demographics and selected risk factors of ESCC and conducted a brief physical examination on the participants. These factors included age, sex, ethnic origin, place of residence, oral health, smoking, alcohol consumption, nass chewing, opium consumption, consumption of fresh fruit, fresh vegetables, pickles, smoked fish, possession of refrigerators and family history of esophageal cancer. We have now analyzed this cross-sectional survey to look for selected factors that could be associated with squamous dysplasia, the precursor lesion of ESCC.

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Table I. *Numbers, percentages, and odds ratios (95% confidence intervals) for selected risk factors for esophageal squamous dysplasia, compared with benign histology.*

Variable	Cases, N(%)	Controls, N(%)	Adjusted OR[1] (95% CI)
Age (10-year increments)	-	-	1.26 (0.96–1.68)
Sex (male *vs.* female)	60 (49%)	25 (50%)	0.93 (0.46–1.88)
Ethnic origin (Turkoman *vs.* Non-Turkoman)	71 (58%)	30 (60%)	1.07 (0.53–2.16)
Place of residence (Turkoman *vs.* outside Turkoman region)	114 (93%)	44 (88%)	2.58 (0.76–8.77)
Oral health			
- Good (Reference)	23 (19%)	18 (36%)	1.00
- Fair	30 (25%)	15 (30%)	1.95 (0.75-5.04)
- Poor	19 (15%)	7 (14%)	2.17 (0.72-6.56)
- Very poor	12 (10%)	3 (6%)	3.62 (0.77-17.0)
- Dental prosthesis	38 (31%)	7 (14%)	4.76 (1.48-15.31)
Smoking (yes *vs.* no)	13 (12%)	7 (14%)	0.96 (0.46–2.02)
Alcohol consumption (yes *vs.* no)	6 (5%)	1 (2%)	3.22 (0.36-29.17)
Nass chewing (a chewing tobacco mixture) (yes *vs.* no)	6 (5%)	4 (2%)	1.04 (0.19-5.61)
Opium consumption (yes *vs.* no)	7 (6%)	3 (6%)	0.89 (0.22-3.66)
Fresh fruits (weekly *vs.* less often)	110 (92%)	40 (82%)	3.18 (1.14-8.90)
Fresh vegetables (weekly *vs.* less often)	91 (74%)	37 (74%)	1.22 (0.54-2.75)
Pickles (yes *vs.* no)	50 (41%)	21 (43%)	0.94 (0.48-1.84)
Smoked fish (yes *vs.* no)	17 (14%)	5 (10%)	1.44 (0.50-4.15)
Refrigerator (10- year increments in having a refrigerator)	-	-	0.92 (0.64-1.30)
Family history of esophageal cancer (yes *vs.* no)	16 (13%)	20 (10%)	0.60 (0.25-1.41)

[1]Adjusted for age, sex, and ethnic origin (for age, sex, and ethnic origin, adjustment has been done only for the two other variables.)

Details of the balloon cytology/chromoendoscopy screening have been published previously (6). Briefly, the town of Bandar-e Turkoman and three nearby villages were selected and all the adults >= 30 years of age were invited to participate. In total, 4192 asymptomatic individuals (20% of the target population) were enrolled. All the subjects were intubated with a balloon exfoliative cytology sampler. From each intubation, smeared slides were prepared and cytological diagnoses were made using the diagnostic categories of the Bethesda System (7). Participants with atypical squamous cells of undetermined significance (ASCUS) or worse diagnoses were invited to undergo video-endoscopic examination enhanced by iodine staining. The mucosal lining of the esophagus and stomach was inspected and gross abnormalities or suspicious lesions before or after staining were biopsied. Standard biopsies were also taken from the posterior aspect of the esophageal mucosa at different sites. The biopsies were read by pathologists unaware of the patients' risk factors, cytologic or endoscopic findings. Histological diagnostic categories were normal epithelium, benign abnormalities, dysplasias (mild, moderate and severe) and invasive cancer.

Of the 4192 individuals (age range=30-88 yrs), the 253 who had cytology diagnoses of ASCUS or worse were invited for a chromo-endoscopic evaluation. Among these, 183 (72%) were endoscoped. For the current analysis, all the individuals with a biopsy showing squamous dysplasia were considered as cases (n=124), and participants with normal histology or benign abnormalities were considered as controls (n=50). Individuals who refused to complete questionnaire data (n=6) and cases with invasive cancer (n=3) were excluded.

For continuous variables, means and standard deviations (SD) were calculated. For categorical variables, frequencies and percentages were calculated. In bivariate analyses, we used the *t*-test to compare means of continuous variables and the Chi-square test to compare frequency of categorical between cases and controls. We used multiple logistic regression models to calculate odds ratios for the association between selected predictors of ESCC and the presence of esophageal squamous dysplasia, adjusting for age, sex, and ethnic origin. Cuzick's test was used to test for a trend in the association between oral hygiene and risk of dysplasia. All *p*-values are two-sided.

Results

One hundred and seventy-four subjects (124 cases and 50 controls) were enrolled in this study. Mean (SD) age in cases and controls were 47.2 (14.3) and 43.1 (12.2) (p-value=0.09). Sixty (49%) of cases and 25 (50%) of controls were males (p-value=0.93). Seventy-one (58%) of cases and 30 (60%) of controls were of Turkoman descent (p-value=0.83).

The adjusted odds ratios for selected predictors of esophageal squamous dysplasia were calculated (Table I). Of the factors evaluated in this study, only poor oral health, assessed in an ordinal scale (good, fair, poor, very poor, dental prosthesis), and higher consumption of fresh fruits were significantly associated with an increased risk of squamous dysplasia (Table I). The association between poor oral health and squamous dysplasia showed a dose-response relationship (p for trend < 0.01).

Discussion

Two reports have previously suggested poor oral health as a risk factor for ESCC in high-incidence areas of China (Linxian County and Shanxi Province) (8,9). However, to our knowledge, this is the first report of an association between poor oral health and a higher risk of premalignant esophageal squamous lesions. One interesting feature of this association was the observed graded association; risk increased gradually with poorer degrees of oral health. There are several ways by which poor oral health might increase the risk of ESCC: (a) physical irritation and damage to the esophageal epithelium due to swallowing unchewed food; (b) change in dietary patterns and nutrient intake due to poor dentition; (c) changes in oral flora with an increase in carcinogen-producing microorganisms; (d) infection of the esophageal mucosa with an oral microorganism; (e) genetic factors that affect both oral health and ESCC. Our data were not detailed enough to distinguish among these possibilities.

In Western countries, ESCC is by far more common in men than in women, and smoking and alcohol consumption are the two main etiologies of this disease (10,11). In high-risk areas of China and Iran, however, ESCC is almost equally common among men and women and smoking and alcohol consumption are not the main risk factors (4,12-14). Consistent with other reports from Iran and China, we did not find an association between sex, smoking, alcohol consumption, or ethnic origin with risk of squamous dysplasia (12-14).

The positive association between consumption of fresh fruit and increased risk of squamous dysplasia was surprising, since most previous studies have shown a null or negative association between fresh fruit consumption and risk of ESCC (15). This association may be confounded by unknown factors or may be due to chance. We also acknowledge that our dietary questions were only about recent use of food items and may not correctly reflect life-long consumption of these food items.

Most of the other suggested risk factors in the previous epidemiological studies in the Caspian Littoral were not associated with a higher risk of ESCC in the subsequent case-control study or with the risk of dysplasia in our analysis (4,5).

The results of this study are consistent with other reports that have shown an association between poor oral health and the risk of esophageal squamous cell carcinoma. Although a few potential risk factors for development of ESCC in high-risk populations have been proposed, none appear to fully explain the extremely high incidence rates of ESCC in northeastern Iran, alone or in combination. Additional careful epidemiological studies are needed to build on the excellent studies started three decades ago to elucidate the causes of EC in this high-risk region.

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